

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 0 739 626 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
07.08.2002 Bulletin 2002/32

(51) Int Cl.7: **A61K 9/70**(21) Application number: **96106759.2**(22) Date of filing: **29.04.1996****(54) Release controlled transdermal therapeutic system**

Transdermales therapeutisches System mit kontrollierter Wirkstofffreisetzung
Système thérapeutique transdermique de libération contrôlée

(84) Designated Contracting States:
DE FR GB IT

(30) Priority: **28.04.1995 JP 12930595**
15.03.1996 JP 8764696

(43) Date of publication of application:
30.10.1996 Bulletin 1996/44

(73) Proprietor: **LEAD CHEMICAL COMPANY LTD.**
Toyama-ken (JP)

(72) Inventor: **Mori, Masao**
Toyama-shi, Toyama-ken (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Arabellastrasse 4
81925 München (DE)

(56) References cited:
EP-A- 0 186 019 **EP-A- 0 241 806**
EP-A- 0 439 180

- **DATABASE WPIL, no. 93-185 162, DERWENT PUBLICATIONS LTD., London; & JP-A-05 112 447 (NISSEI TECHNICA KK)**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 739 626 B1

1

EP 0 739 626 B1

2

Description**FIELD OF THE INVENTION**

[0001] The present invention relates to a transdermal therapeutic system in which the release rate of drugs can optionally be controlled according to the purposes of therapeutics, having extremely excellent in storage stability, and also having high safety, being free from dermatitis or the like due to adhesion of the preparation.

BACKGROUND OF THE INVENTION

[0002] Adhesive preparations comprising natural or synthetic rubber type adhesives as a main component have disadvantages where changes on preparation, such as a decrease in drug content due to decomposition and volatilization of the drugs and a decrease in adhesive strength, are liable to occur, and storage stability of the preparation is poor.

[0003] Further, since the rubber-type adhesives do not absorb moisture, preparations comprising such adhesives may cause perspiration, or a peel off from a skin tends to occur when the skin has a high moisture at the time of adhesion. Also, in the case where the preparation has a high sealing property, dermatitis may be caused on the skin due to sodden state on the skin. Where the adhesive has less air permeability or no permeability when the adhesive preparation is used, corneous cells at the adhered portion are sealed, resulting in sodden and perhydrated state due to the moisture of skin. On the other hand, since dried skin surface layer is brittle, the skin peels at the portion where the surface layer is weakened upon peeling off the adhesive preparation from the skin. If the adhesive preparation is repeatedly adhered to the same portion under such a state, a corneous layer is destroyed, and erythema is caused due to expansion of blood vessels to cause an eruption, resulting in dermatitis. Further, the conventional transdermal therapeutic systems have disadvantages that they are well adhered to the dried and less fatty skin of old person, but have a low adhesive force to a fatty skin or a wet skin.

[0004] As a transdermal therapeutic system containing microcapsule, JP-B-2-38569 (Japanese patent publication: Hei 2-28569) proposes a system in which microcapsules that contain as a core material an absorption accelerator are dispersed in an adhesive layer, and a wall material thereof swells by skin moisture upon the adhesion to the skin, thereby the absorption accelerator diffuses into the adhesive layer. As a result, transdermic absorption of drugs contained in the adhesive layer is accelerated. In the above invention, it is believed that since skin moisture is not absorbed in a synthetic rubber type adhesive layer which is hydrophobic, the microcapsules to be swollen are restricted to the only microcapsules which are on the surface of the adhesive layer, and also since drugs are dispersed or dissolved in the

adhesive layer, the system is poor in the storage stability by the mutual action between the drug components.

[0005] JP-A-3-163013 (Japanese Patent Laid Open Hei-163013) proposes an antipruritic microcapsule containing drugs as a core material and having a wall material comprising formalin resin as a main component. In the invention described in JP-A-3-163013, it is believed that the system has a high safety, but the wall material must be broken by physical friction from the outside.

[0006] PCT Publication Hei 4-503810 proposes a transdermal therapeutic system having microreserver materials of estrogen dispersed therein, but it is not believed that destruction of wall material and also diffusion of the core material are sufficient.

[0007] In those prior arts, the system has a poor storage stability, and it is impossible to control a release rate of the drugs.

[0008] The requirements for an excellent medical adhesive preparation include that the decreases in drug content and in adhesive strength do not occur, the storage stability is excellent, a moderate adhesive strength is maintained upon the adhesion even to a wet skin due to sweat or the like, and a skin is not damaged when peeling off the preparation.

[0009] It is desirable for the transdermal therapeutic system, particularly important requirements, to have a high drug absorbability and to be able to control a release rate of the drug according to the purposes of therapeutics.

SUMMARY OF THE INVENTION

[0010] Various studies have been made to overcome the problems in the conventional system that use a natural or a synthetic rubbery adhesive, and an object of the invention is to develop an excellent transdermal therapeutic system the release amount of which can optionally be controlled.

[0011] As a result, it has been found in the present invention that an adhesive preparation having high storage stability can be obtained by dispersing in a rubbery adhesive in a transdermal therapeutic system using the rubbery adhesive, microcapsules comprising water-soluble wall material and encapsulating drugs or drugs and an absorption accelerator as core material, so that the drugs are separated from the rubbery adhesive.

[0012] It has also been found that a release rate of drugs can optionally be controlled by mixing several kinds of microcapsules having different wall thickness and particle size distribution. Further, it has been found that the problems involved in the conventional rubbery adhesive can be overcome by dispersing water-insoluble, rubber- and rubber solvent-insoluble, water absorbing resin powder, and water-soluble resin powder in the adhesive to absorb sweat secreted from the skin when adhering the adhesive.

[0013] The release amount and the release rate of the

3

EP 0 739 626 B1

4

drugs from the microcapsules dispersed in the rubbery adhesive depend on the concentrations of microcapsules, water absorbing resin powder and water-soluble polymer powder, the thickness of the wall material of a microcapsule, the size of a microcapsule particle, and the like, and are adjusted by controlling those factors. In particular, the release amount and the release rate of the drugs with the passage of time are controlled by using a mixture of microcapsule particles having different wall material thickness and/or microcapsule particles having different particle size distribution.

[0014] According to a first embodiment of the present invention, there is provided a release controlled transdermal therapeutic system comprising a rubbery adhesive, microcapsules comprising a water-soluble wall material and encapsulating drugs as core material, and a water-insoluble, rubber- and rubber solvent-insoluble, water absorbing resin powder, the microcapsules and the resin powder being dispersed in the rubbery adhesive.

[0015] According to a second embodiment of the present invention, there is provided a release controlled transdermal therapeutic system comprising a rubbery adhesive, microcapsules comprising a water-soluble wall material and encapsulating drugs as core material, a water-insoluble, rubber- and rubber solvent-insoluble, water absorbing resin powder, and a water-soluble polymer powder having adhesion in the presence of moisture, the microcapsules, the resin powder and the polymer powder being dispersed in the rubbery adhesive.

[0016] According to a third embodiment of the present invention, there is provided a release controlled transdermal therapeutic system comprising the release controlled transdermal therapeutic system of the above first or second embodiment which further comprises at least two or more kinds of microcapsule particles having different wall material thicknesses and/or at least two or more kinds of microcapsule particles having different particle size distributions which are mixed therewith.

[0017] The present invention also relates to a tape preparation or a patch type adhesive preparation using those systems.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018]

Fig. 1 is an explanatory view of a adhesive layer in a tape preparation according to the present invention;

Fig. 2 is a cross-sectional view of the tape preparation according to the present invention;

Fig. 3 is an explanatory view of a adhesive layer in one embodiment of a patch type adhesive preparation according to the present invention;

Fig. 4 is a cross-sectional view of the patch type adhesive preparation according to the present invention;

Fig. 5 is an explanatory view of the adhesive layer in another embodiment of the patch type adhesive preparation according to the present invention; and Fig. 6 is a cross-sectional view of further another embodiment of the patch type adhesive preparation according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The transdermal therapeutic system according to the present invention makes it possible to increase the storage stability of the system and to optionally control the release rate of drugs by microencapsulation of drugs, or drugs and an absorption accelerator.

[0020] When adhering the transdermal therapeutic system, a water absorbing resin powder dispersed in the adhesive absorbs body fluid such as sweat inside the adhesive to remove the retention of egesta such as sweat at the interface between the skin and the adhesive, thereby peeling off from the skin surface rarely occurs. Simultaneously, the water-soluble wall material of the microcapsules is destroyed by the absorbed moisture, and drugs, or drugs and absorption accelerator, contained in the microcapsules, are eluted and diffused in the adhesive. Further, the water-soluble polymer powder dispersed in the base material has a function to impart adhesive properties to a system in the presence of water, and as a result, a transdermal therapeutic system which does not peel stratum corneum and is difficult to cause dermatitis can be obtained.

[0021] In the site sealed by the adhesive preparation of the present invention, the stratum corneum softens and swells, thereby a barrier property of the site is decreased, and consequently, transdermic absorption of drugs is markedly increased.

[0022] The rubbery adhesive used in the present invention comprises a rubber adhesive component, a tackifier component, and a plasticizer component.

[0023] Examples of the rubbery adhesive component that can be used in the present invention include natural rubbers; isoprene rubbers; styrene copolymer rubbers such as isobutylene rubbers, styrene-butadiene rubber, styrene-butadiene-styrene block copolymer, or styrene-isoprene-styrene block copolymer; silicone rubbers; and acrylic rubbers. Those rubbers can be appropriately selected, and can also be used alone or as a mixture of two or more thereof.

[0024] Examples of the tackifier component that can be used in the present invention include petroleum resins, rosins, hydrogenated rosins, ester gums, terpene resins, modified terpene resins, coumarone-indene resins, petroleum cracking fractions, aromatic hydrocarbon resins, styrene resins and isoprene resins. Those can appropriately be selected, and also can be used alone or as a mixture of two or more kinds thereof,

[0025] The amount of the tackifier component used is from 40 to 200 parts by weight, and preferably from 60 to 100 parts by weight, per 100 parts by weight of the

5

EP 0 739 626 B1

6

rubber adhesive component.

[0026] Examples of the plasticizer component that can be used in the present invention include poly-butenes, low molecular weight poly-isobutylenes, vaseline, lanolin, liquid paraffin, higher fatty acid esters, vegetable oils, and animal oils. Those can appropriately be selected, and also can be used alone or as a mixture of two or more thereof.

[0027] The amount of the plasticizer component used is from 30 to 300 parts by weight, and preferably from 70 to 250 parts by weight, per 100 parts by weight of the rubber adhesive component.

[0028] Natural rubbers and synthetic rubbers used for the rubber adhesive component have unsaturated bonds in the molecule, and, therefore, have the possibility to deteriorate upon exposure to oxygen or ultraviolet rays. Therefore, it is preferred for the rubbery adhesive to contain stabilizers such as antioxidant, UV absorber and the like, for example, dibutylhydroxyphenyl, or 4-ethyl-6-butylphenol.

[0029] In the present invention, drugs are mixed with and dispersed in the rubbery adhesive in the form of microcapsules.

[0030] The drugs that can be used in the present invention are oily materials that do not dissolve the wall material. Examples of the drugs that can be used include methyl salicylate, glycol salicylate, 1-menthol, di-menthol, di-camphor, d-borneol, peppermint oil, cayenne pepper extract, vanillylamide nonylate, diphenhydramine salicylate, nitroglycerin, isosorbide dinitrate, flurbiprofen, ketoprofen, indomethacin, loxoprofen sodium, ibuprofen, dichlofenac, mefenamic acid, chlorpheniramine d-maleate, chlorpheniramine di-maleate, diphenhydramine salicylate, diphenhydramine, progesterone, testosterone, estriol, estradiol, ethynyl estradiol, propranolol, tolubutanol, scopolamine, tranilast, ketotifen fumarate, bectometanone propionate, atropine, and lidocaine. Those can appropriately be selected, and also can be used alone or as a mixture of two or more kinds thereof.

Further, the drugs are not limited to the materials as described above.

[0031] The wall material of the microcapsules comprises a water-soluble polymeric material. Examples of the wall material of microcapsules include gelatin, gum arabic, polyvinyl alcohol, and carboxymethyl cellulose. Those can be used alone or as a mixture of two or more kinds thereof. The wall thickness of the microcapsules is adjusted by changing the preparation conditions such as a mixing ratio of a core material and the wall material, a curing time of the microcapsules, thereby the release rate of drugs from the system can be controlled. Further, the release rate of the drugs can optionally be controlled by mixing two or more kinds of microcapsules having different wall thickness.

[0032] If the particle size of the microcapsules is too small, the amount of the drugs to be contained in the microcapsule decreases. On the other hand, if the par-

ticle size of the microcapsule is too large, destruction of the microcapsule particles occurs in the steps, which are mixing the particles with the adhesive, applying the resulting mixture to a base fabric, and drying the coated mixture. Also, the stability of the system cannot be obtained. Therefore, the particle size of the microcapsule is preferably in the range of from about 1 to 100 μm .

[0033] Similarly, if the wall thickness of the microcapsule is less than 0.2 μm , the microcapsules are liable to destroy, and on the other hand, if the wall thickness is larger than 2 μm , it is difficult to destroy the microcapsule film (wall of microcapsule), and elution of the core material from the microcapsule becomes slow. Therefore, the wall thickness of the microcapsule is preferably in the range of from about 0.2 to 2 μm . Further, the weight proportion of the core material in the microcapsule is preferably from 85 to 90%.

[0034] Microcapsules having various particle sizes and wall thicknesses can be obtained by adjusting microcapsules in the way such that one polymeric material or a mixture of two or more polymeric materials is used, and that conditions such as types of the core material and the wall material, the mixing ratio thereof, gelation time of the microcapsules are changed. It is possible to disirably control the release rate of the drugs by mixing two or more thus obtained microcapsules having different particle sizes and different wall thickness. That is, the microcapsules having a small wall thickness are easily destroyed by a slight amount of moisture absorption after adhesion, and the release of the drugs becomes fast. On the other hand, the microcapsules having a large wall thickness results in slow release of the drugs. Therefore, it is possible to optionally control the release rate of the drugs by adjusting the wall thickness of the microcapsules according to the purposes of therapeutics.

[0035] The core material of the microcapsule comprises drugs, and can further comprises an absorption accelerator. By containing the absorption accelerator, systems having excellent storage stability and high drug absorption property can be obtained.

[0036] The absorption accelerator that can be used in the present invention is materials that do not dissolve the wall material. Examples of the absorption accelerator include aliphatic alcohols having 10 to 22 carbon atoms, aliphatic carboxylic acids having 9 to 22 carbon atoms, aliphatic amines, long chain aliphatic esters, N-alkyllactum, crotamiton, and monoterpene compounds. Those compounds are appropriately selected, and also can be used alone or as a mixture of two or more kinds thereof.

[0037] Examples of the water absorbing resin powder that can be used in the present invention include starch-polyacrylate graft copolymer ("SUNWET", a product of Sanyo Chemical Industry Co.), crosslinked polyacrylates ("ARASOAP", a trade name, a product of Arakawa Chemical Industry Co.; "AQUAKEEP", a trade name, a product of Seitetsu Chemical Industry Co.;

7

EP 0 739 626 B1

8

"AQUALICR", a trade name, a product of Nippon Shokubai Chemical Industry Co.), acrylic acid-vinyl alcohol copolymers ("SUMIKAGEL S TYPE", a trade name, a product of Sumitomo Chemical Co.), polyethylene oxide crosslinked product ("SUMIKAGEL R TYPE", a trade name, as product of Sumitomo Chemical Co.), and crosslinked isobutylene-maleate copolymer ("KIGEL", a trade name, a product of Kuraray Co.).

Those water absorbing resins are resins having three-dimensional structure obtained by appropriately crosslinking water-soluble resins. Those resins contain hydrophilic groups such as hydroxyl group, carboxylic acid group, carboxylic acid salt group in the molecule, and therefore have a high water absorption ability. It is preferred for the water absorbing resin to have high water absorption ability of at least 100 g/g as deionized water.

[0038] Those water absorbing resins can be used alone or as a mixture of two more same or different kinds of resins having different particle sizes.

[0039] The water absorbing resin powder has an average particle size of from 1 to 100 μm , and preferably from 5 to 30 μm .

[0040] The water absorbing resin is used in an amount of from 0 to 30% by weight, and preferably from 5 to 20% by weight, based on the weight of the rubbery adhesive.

[0041] Examples of the water-soluble polymer powder having an adhesiveness in the presence of water which can be used in the present invention include powders of polyacrylic acid, polyacrylic acid salt, polyacrylamide, polyethylene oxide, polyethylene imine, polyvinyl alcohol, polyvinyl chloride, polyvinyl pyrrolidone, carboxyvinyl polymer, methyl cellulose, carboxymethyl cellulose, and hydroxyethyl cellulose. Those powder can be used alone or as a mixture of two or more same or different kinds of powder having different particle sizes.

[0042] The water absorbing polymer powder has an average particle size of from 1 to 100 μm , and preferably from 5 to 30 μm .

[0043] The water absorbing polymer powder is used in an amount of from 0 to 30% by weight, and preferably from 5 to 20% by weight, based on the weight of the rubbery adhesive.

[0044] The transdermal therapeutic system according to the present invention can be used in any optional form such as a tape preparation, and a patch type adhesive preparation.

[0045] Fig. 1 is a view explaining a layer obtained by applying a dispersion to a base fabric or a release paper in a tape preparation. and Fig. 2 is a cross-sectional view of the tape preparation. In those Figures, 1 is an adhesive layer, 2 is microcapsules, 3 is a water absorbing resin powder, 4 is a base fabric, and 5 is a release paper.

[0046] The tape preparation can be produced by the following method. The rubbery adhesive comprising a rubber adhesive component, a tackifier, and a plasticizer is dissolved in a volatile organic solvent, the micro-

capsule 2 containing drugs and comprising a water-soluble wall material, and the water-insoluble, rubber- and rubber solvent-insoluble water absorbing resin powder 3 are dispersed in the solution obtained above, the resulting dispersion is applied to the base fabric 4 or the release paper 5, the organic solvent is volatilized to form the adhesive layer 1, in which the microcapsule 2 and the water absorbing resin powder 3 are dispersed, and the release paper 5 or the base fabric 4 is laminated on the adhesive layer 1, respectively.

[0047] Figs. 3 and 4 show another embodiment of the patch type adhesive preparation, and Figs. 5 and 6 show further another embodiment of the patch type adhesive preparation. In those patch adhesive preparations, the adhesive can be prepared in the same manner as in the tape preparation that the rubbery adhesive comprising the rubber adhesive component, the tackifier, and the plasticizer is dissolved in a volatile organic solvent, and that the microcapsule 2 containing drugs and comprising the water-soluble wall material 2, and the water-soluble, rubber- and rubber solvent-soluble, water absorbing resins powder 3 are dispersed in the solution obtained above.

[0048] The patch type adhesive preparation can be prepared by the following manner. The adhesive is applied to a part such as a central portion of the base fabric 4 or the release paper 5 to form the adhesive layer 1 having the microcapsule 2 and the water absorbing resin powder 3 dispersed therein, and the adhesive layer 6 which does not contain microcapsules is applied to the remaining portion, such as the circumferential portion of the base fabric 4 or the release paper 5, as shown in Figs. 3 and 4. Alternatively, the adhesive layer which does not contain the microcapsules is formed on the base fabric 4 or the release paper 5, and the adhesive layer containing the microcapsule 2 and the water absorbing resin powder 3 dispersed therein is then laminated on the adhesive layer 6, as shown in Figs. 5 and 6.

[0049] The adhesive can be applied by any coating method such as hot pressing method (calendar coating), hot melt method (hot melt coating), or solution coating. When the wall thickness of the microcapsule is small, the calendar coating and the hot melt coating involve the destruction of particles. Therefore, when the microcapsules having a small wall thickness are used, the solution coating is preferably employed. A solvent that can be used in the solution coating is preferably a solvent having a high dissolution property of natural rubber and synthetic rubbers, and the examples thereof include toluene, n-hexane, isohexane, cyclohexane, and a volatile oil for rubber.

[0050] The base fabric that can be used in the present invention is woven fabrics or non-woven fabrics, such as polyvinyl chloride films, polyester films, polyolefin films, laminated films of polyvinyl chloride films and polyester films, polyester films, polypropylene films, or rayon films; films obtained by hot welding the non-woven fabrics on the polyester films; or the like.

9

EP 0 739 626 B1

10

[0051] The present invention is described in more detail with reference to the following Examples, but it should be understood that the invention is not construed as being limited thereto. Unless otherwise indicated, all parts, percents, ratios, and the like are by weight.

EXAMPLE 1

Preparation of Microcapsules:

[0052] 250 Parts of a 5% polyvinyl alcohol aqueous solution, 250 parts of 5% carboxymethyl cellulose aqueous solution, 80 parts of flurbiprofen, and 50 parts of sorbitan sesquioleate were mixed with stirring to form o/w type emulsion. Temperature of the emulsion was raised to 40 °C, and 250 parts of a 2.5% sodium chloride were gradually added thereto.

The resulting mixture was cooled to 10 °C, and 20 parts of a 50% glutaraldehyde were added thereto. The resulting mixture was stirred for 15 hours, was heated to 40 °C, and was further stirred for 3 hours. The mixture was washed, filtered off, and spray dried. Microcapsules thus obtained had a concentration of a core material of 87%, a concentration of a drug (flurbiprofen) contained of 47.1%, and an average particle size of 16 µm,

Production of Transdermal Therapeutic System :

[0053] 30 Parts of a styrene-isoprene-styrene block copolymer, 10 parts of a polyisobutylene, 20 parts of liquid paraffin, and 30 parts of a tackifier (ESCORETS 5300) were dissolved in 350 parts of n-hexane.

[0054] 3 Parts of the microcapsules obtained above, 5 parts of 100 mesh pass starch-polyacrylic acid graft copolymer, and 5 parts of 100 mesh pass polyacrylic acid powder (HIVISWAKOGEL) were dispersed in the adhesive solution obtained above. The resulting dispersion was coated on a release paper, and heated to evaporate n-hexane. A vinyl chloride film was laminated on the coating layer to obtain a transdermal therapeutic system.

EXAMPLE 2

Preparation of Microcapsule (I):

[0055] 20 Parts of clotamiton, 20 parts of butylene glycol, and 10 parts of ethynyl estradiol were dispersed and emulsified in 30 parts of a 10% gelatin aqueous solution to form an o/w type emulsion, 30 Parts of a 10% gum arabic aqueous solution were added to the emulsion, followed by stirring for about 20 minutes, 200 Parts of 40°C hot water were added to the mixture, and pH of the resulting mixture was adjusted to 4 to 4.3 with 10% acetic acid. After formation of a sol, the sol was cooled to 5°C to form a gel. 1 Part of 30% formalin was added to the gel, and 10% sodium hydroxide was added drop-let thereto to adjust the pH to 9. The mixture was grad-

ually heated and stirred at 50 °C for about 1 hour. The mixture was washed with water, filtered off, and spray dried to obtain spherical microcapsules having a concentration of a core material of 89%, a concentration of a drug (ethynyl estradiol) contained of 12.7%, and an average particle size of 13µm.

Preparation of Microcapsule (II):

[0056] 15 parts of clotamiton, 20 parts of butylene glycol, and 15 parts of ethynyl estradiol were dissolved in 40 parts of a 12.5% gelatin aqueous solution to form an o/w type emulsion. 30 Parts of a 10% gum arabic aqueous solution were added to the emulsion, followed by mixing for about 20 minutes. After adding 200 parts of 40°C hot water to the mixture, pH of the resulting mixture was adjusted with a 10% acetic acid to 4 to 4.3 to form a sol. The sol was cooled to 5 °C to form a gel. 1 Part of 30% formalin was added to the gel, and 10% sodium hydroxide was added dropwise thereto to adjust the pH to 9. The mixture was gradually heated, and stirred at 50 °C for about 1 hour. The resulting mixture was washed, filtered off, and spray dried to obtain spherical microcapsules having a concentration of a core material of 76%, a concentration of drug (ethynyl estradiol) of 15.1%, and an average particle size of 16 µm.

Production of Transdermal Therapeutic system :

[0057] 25 Parts of a styrene-Isoprene-styrene block copolymer, 15 parts of polyisobutylene, 25 parts of liquid paraffin, and 25 parts of a tackifier (ESCORET 5300) were mixed with and dissolved in 340 parts of n-hexane to prepare a adhesive solution. 2 Parts of the microcapsule (I) obtained above, 3 parts of the microcapsule (II) obtained above, and 7 parts of 100 mesh pass starch-polyacrylic acid salt graft copolymer (SUNWET M1000) were mixed with and dispersed in the adhesive solution. The resulting dispersion was coated on a release paper, and heated to evaporate n-hexane to form a adhesive layer. A vinyl chloride film was laminated on the surface of the adhesive layer to obtain a transdermal therapeutic system.

Claims

1. Release controlled transdermal therapeutic system comprising
 - i) a rubbery adhesive;
 - ii) microcapsules comprising a water-soluble wall material encapsulating at least one oily drug as core material which does not dissolve the wall material; and
 - iii) a water-insoluble, rubber- and rubber sol-

11

EP 0 739 626 B1

12

vent-insoluble, water absorbing resin powder, optionally together with a rubber- and rubber solvent-insoluble, water-soluble polymer powder having an adhesion in the presence of moisture;

wherein the microcapsules and the resin/polymer powder(s) are dispersed in the rubbery adhesive.

2. Therapeutic system according to claim 1, wherein the rubbery adhesive comprises

i) at least one component selected from natural rubbers, isoprene rubbers, isobutylene rubbers, styrene copolymer rubbers, silicone rubbers and acrylic rubber;

ii) at least one tackifier selected from petroleum resins, rosins, hydrogenated rosins, ester gums, terpene resins, modified terpene resins, coumarone-indene resins, petroleum cracking fractions, aromatic hydrocarbon resins, styrene resins and isoprene resins; and

iii) at least one plasticizer selected from polybutenes, low molecular weight polyisobutylenes, vaseline, lanolin, liquid paraffin, higher fatty acid esters, vegetable oils, and animal oils.

3. Therapeutic system according to claim 1 or 2, wherein the water absorbing resin powder is selected from starch-polyacrylic acid salt graft copolymers, crosslinked polyacrylic acid salts, acrylic acid-vinyl alcohol copolymers, polyoxyethyleneoxide crosslinked products, or crosslinked isobutylene-maleic acid salt copolymers, each having an average particle size of 1-100 μm .

4. Therapeutic system according to any of the preceding claims, wherein the wall material comprises at least one selected from gelatin, gum arabic, polyvinyl alcohol, and carboxymethyl cellulose.

5. Therapeutic system according to any of the preceding claims comprising at least two kinds of microcapsules having different wall thickness.

6. Therapeutic system according to any of the preceding claims, wherein the microcapsules have an average particle size of 100 μm or less.

7. Therapeutic system according to any of the preceding claims, wherein the microcapsules further comprise, as a core material, an absorption accelerator comprising at least one selected from aliphatic C_{10-22} alcohols, aliphatic C_{9-22} carboxylic acids, aliphatic amines, long chain aliphatic esters, N-alkyl

lactam, crotonamiton, and monoterpene compounds.

8. Adhesive preparation comprising a base fabric and, provided thereon, a layer of the therapeutic system according to any of claims 1-7.

9. Adhesive preparation according to claim 8, wherein the layer of the therapeutic system according to any of the claims 1-7 only partially covers the base fabric.

10. Adhesive preparation according to claim 9, wherein a further layer of a rubbery adhesive not containing microcapsules is present on the base fabric such that it is provided between the base fabric and the layer of the therapeutic system according to claims 1-7 or such that it covers that part of the base fabric where the therapeutic system is not coated.

11. Adhesive preparation according to any of claims 8-10 further comprising a release paper provided on the layer of the therapeutic system of any of claims 1-7.

12. Adhesive preparation according to any of claims 8-11 wherein the base fabric is selected from woven fabrics, non-woven fabrics selected from PVC films, polyester films, polyolefin films, laminated films of PVC and polypropylene films or rayon films, and films obtained by hot welding non-woven fabrics on a polyester film.

Patentansprüche

1. Freisetzungsgesteuertes transdermales, therapeutisches System, das folgendes umfasst:

(i) einen gummiartigen Klebstoff;

(ii) Mikrokapseln, die ein wasserlösliches Wandmaterial umfassen, das mindestens einen öligen Wirkstoff als Kernmaterial, der das Wandmaterial nicht auflöst, einkapseln; und

(iii) ein wasserunlösliches Gummi- und Gummilösungsmittel-unlösliches wasserabsorbierendes Harzpulver, gegebenenfalls zusammen mit einem Gummi und Gummilösungsmittel-unlöslichen wasserlöslichen Polymerpulver, das in Gegenwart von Feuchtigkeit Adhäsion zeigt;

worin die Mikrokapseln und das Harz-Polymerpulver in dem gummiartigen Klebstoff dispergiert sind.

2. Therapeutisches System gemäß Anspruch 1, worin der gummiartige Klebstoff folgendes umfasst:

13

EP 0 739 626 B1

14

(i) mindestens eine Komponente, ausgewählt aus natürlichen Gummi, Isoprengummi, Isobutylengummi, Styrol-Copolymergummi, Silicongummi und Acrylgummi;

(ii) mindestens einen Klebrigmacher, ausgewählt aus Petroleumharzen, Kollophoniumharzen, hydrierten Kollophoniumharzen, Ester-gummi, Terpenharzen, modifizierten Terpenharzen, Coumaronindenharzen, Petroleum-crackingfraktionen, aromatischen Kohlenwasserstoffharzen, Styrolharzen und Isoprenharzen; und

(iii) mindestens einen Weichmacher, ausgewählt aus Polybutenen, niedermolekulargewichtigen Polyisobutylenen, Vaseline, Lanolin, flüssigem Paraffin, höheren Fettsäureestern, pflanzlichen Ölen und tierischen Ölen.

3. Therapeutisches System gemäß Anspruch 1 oder 2, worin das wasserabsorbierende Harzpulver ausgewählt ist aus Stärke-Polyacrylsäuresalz-Pfropfpolymeren, vernetzten Polyacrylsäuresalzen, Acrylsäure-Vinylalkohol-Copolymeren, Polyoxyethylenoxidvernetzten Produkten oder vernetzten Isobutylen-Maleinsäuresalz-Copolymeren, die jeweils eine durchschnittliche Teilchengröße von 1-100 µm aufweisen.

4. Therapeutisches System gemäß mindestens einem der vorhergehenden Ansprüche, worin das Wandmaterial mindestens eines, ausgewählt aus Gelatine, Gummi arabicum, Polyvinylalkohol und Carboxymethylcellulose, umfasst.

5. Therapeutisches System gemäß mindestens einem der vorhergehenden Ansprüche, das mindestens zwei Arten Mikrokapseln mit unterschiedlichen Wanddicken umfasst.

6. Therapeutisches System gemäß mindestens einem der vorhergehenden Ansprüche, worin die Mikrokapseln eine durchschnittliche Teilchengröße von 100 µm oder weniger aufweisen.

7. Therapeutisches System gemäß mindestens einem der vorhergehenden Ansprüche, worin die Mikrokapseln ferner als ein Kernmaterial einen Absorptionsbeschleuniger umfassen, der mindestens eines, ausgewählt aus aliphatischen C₁₀₋₂₂-Alkoholen, aliphatischen C₉₋₂₂-Carbonsäuren, aliphatischen Aminen, langkettigen aliphatischen Estern, N-Alkylactam, Crotonit und Monoterpenverbindungen umfasst.

8. Adhäsive Zusammensetzung, die ein Grundtextil und darauf aufgebracht eine Schicht aus dem the-

rapeutischen System gemäß mindestens einem der Ansprüche 1 bis 7 umfasst.

9. Adhäsive Zusammensetzung gemäß Anspruch 8, worin die Schicht aus dem therapeutischen System gemäß mindestens einem der Ansprüche 1 bis 7 das Grundtextil nur teilweise bedeckt.

10. Adhäsive Zusammensetzung gemäß Anspruch 9, worin eine weitere Schicht aus einem gummiartigen Klebstoff, die keine Mikrokapseln enthält, auf dem Grundtextil in einer solchen Weise vorhanden ist, dass sie zwischen dem Grundtextil und der Schicht aus dem therapeutischen System gemäß den Ansprüchen 1 bis 7 vorhanden ist, oder in einer solchen Weise, dass sie den Bereich des Grundtextils bedeckt, in dem das therapeutische System nicht aufgeschichtet ist.

11. Adhäsive Zusammensetzung gemäß mindestens einem der Ansprüche 8 bis 10, die ferner ein Ablösepapier umfasst, das auf der Schicht des therapeutischen Systems gemäß mindestens einem der Ansprüche 1 bis 7 bereitgestellt ist.

12. Adhäsive Zubereitung gemäß mindestens einem der Ansprüche 8 bis 11, worin das Grundtextil ausgewählt ist aus gewebten Textilien, Non-woven-Textilien, ausgewählt aus PVC-Folien, Polyesterfolien, Polyolefinfolien, laminierten Folien aus PVC und Polypropylenfolien oder Rayonfolien, und Folien, die erhalten werden durch Heissverschmelzen von Non-woven-Textilien mit einer Polyesterfolie.

Revendications

1. Système thérapeutique transdermique de libération contrôlée comprenant

i) un adhésif en caoutchouc ;

ii) des microcapsules comprenant un matériau de paroi hydrosoluble encapsulant au moins, comme matériau du coeur, une substance médicamenteuse huileuse ne dissolvant pas le matériau de paroi ; et

iii) une poudre de résine absorbant l'eau, insoluble dans l'eau, insoluble dans le caoutchouc et dans un solvant du caoutchouc, avec en option une poudre de polymère hydrosoluble, insoluble dans le caoutchouc et dans un solvant du caoutchouc, et présentant une adhésion en présence d'humidité ;

dans lequel les microcapsules et la(es) poudre(s) de résine/polymère sont dispersées dans l'adhésif en caoutchouc.

15

EP 0 739 626 B1

16

2. Système thérapeutique selon la revendication 1, dans lequel l'adhésif en caoutchouc comprend

i) au moins un composant sélectionné parmi les caoutchoucs naturels, les caoutchoucs isoprènes, les caoutchoucs d'isobutylène, les caoutchoucs de copolymère de styrène, les caoutchoucs de silicone et les caoutchoucs acryliques ;

ii) au moins un agent collant sélectionné parmi les résines de pétrole, les colophanes, les colophanes hydrogénés, les gommes d'esters, les résines de terpènes, les résines de terpènes modifiés, les résines de coumarone-indènes, les fractions de craquage du pétrole, les résines d'hydrocarbures aromatiques, les résines de styrène et les résines d'isoprène ; et

iii) Au moins un plastifiant sélectionné parmi les polybutènes, les polyisobutylènes à faible poids moléculaire, la vaseline, la lanoline, la paraffine liquide, les esters d'acides gras supérieurs, les huiles végétales, et les huiles animales

3. Système thérapeutique selon la revendication 1 ou 2, dans lequel la poudre de résine absorbant l'eau est sélectionnée parmi les copolymères d'amidon et de sel d'acide acrylique greffés, les sels d'acide polyacrylique réticulés, les copolymères d'alcool vinylique et d'acide acrylique, les produits réticulés d'oxydes de polyoxyéthylène, ou les copolymères réticulés d'isobutylène et de sel d'acide maléique, chacune présentant une taille moyenne de particule de 1 à 100 μm

4. Système thérapeutique selon l'une quelconque des revendications précédentes, dans lequel le matériau de paroi comprend au moins un matériau sélectionné parmi la gélatine, la gomme arabique, l'alcool polyvinylique, et la carboxyméthylcellulose.

5. Système thérapeutique selon l'une quelconque des revendications précédentes comprenant au moins deux sortes de microcapsules présentant des épaisseurs différentes de la paroi.

6. Système thérapeutique selon l'une quelconque des revendications précédentes, dans lequel les microcapsules présentent une taille moyenne de particule de 100 μm ou moins.

7. Système thérapeutique selon l'une quelconque des revendications précédentes, dans lequel les microcapsules comprennent en plus, comme matériau du coeur, un accélérateur d'absorption comprenant au moins un matériau sélectionné parmi les alcools aliphatiques en C_{10-22} , les acides carboxyliques aliphatiques en C_{9-22} , les amines aliphatiques, les es-

ters aliphatiques à chaîne longue, le N-alkyle-lactame, le crotamiton, et les composés monoterpènes.

8. Préparation adhésive comprenant une toile de base, et sur laquelle se trouve une couche du système thérapeutique selon l'une quelconque des revendications 1 à 7.

9. Préparation adhésive selon la revendication 8, dans laquelle la couche du système thérapeutique selon l'une quelconque des revendications 1 à 7 ne recouvre que partiellement la toile de base.

10. Préparation adhésive selon la revendication 9, dans laquelle une couche supplémentaire d'adhésif en caoutchouc ne contenant pas de microcapsules est présente sur la toile de base de façon qu'elle se trouve entre la toile de base et la couche du système thérapeutique selon les revendications 1 à 7, ou de façon qu'elle recouvre la partie de la toile de base non recouverte par le système thérapeutique.

11. Préparation adhésive selon l'une quelconque des revendications 8 à 10 comprenant en plus un papier détachable situé sur la couche du système thérapeutique selon les revendications 1 à 7.

12. Préparation adhésive selon l'une quelconque des revendications 8 à 11 dans laquelle la toile de base est sélectionnée parmi les étoffes tissées, les toiles non tissées sélectionnées parmi les films de PVC, les films de polyester, les films de polyoléfine, les films laminés en PVC et les films de polypropylène ou les films de rayonnées, et les films obtenus par soudure à chaud de toiles non tissées sur un film de polyester.

EP 0 739 626 B1

FIG. 1

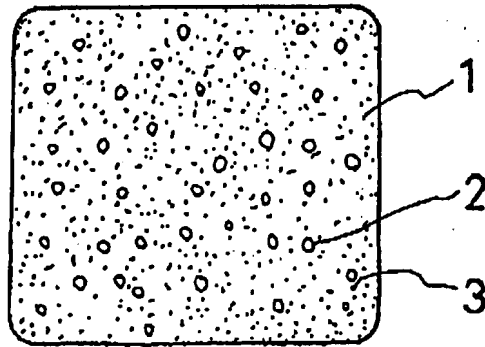


FIG. 2

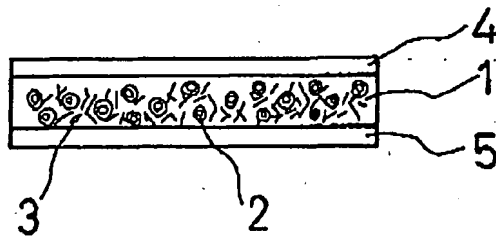
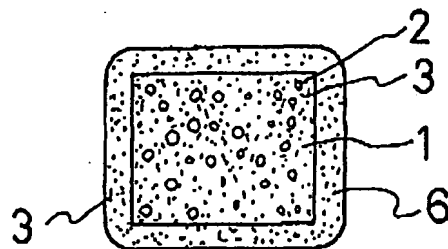


FIG. 3



EP 0 739 626 B1

FIG. 4

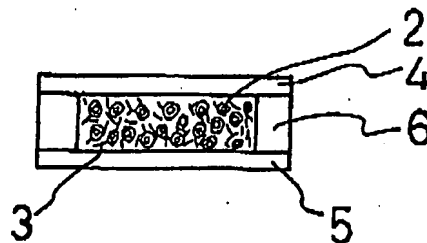


FIG. 5

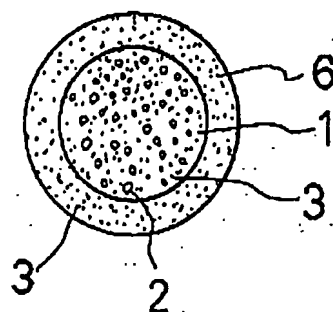


FIG. 6

